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Postoperative Complications After Pneumonectomy for Treatment of Lung Cancer: Multivariate Analysis

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The charts of 62 patients with primary lung cancer who underwent a pneumonectomy at our department from 1979 through 1992 were reviewed for the evaluation of postoperative morbidity and mortality. The 30-day mortality was 3/62 or 4.8%. Postoperative complication occurred in 37 of 62 patients (60%). The most common complication was a supraventricular tachyarrythmia. A major complication, which was defined as one necessitating re-thoracotomy or one which caused death, occurred in 19 patients (31%). We analyzed 43 perioperative variables for their predictive value of postoperative morbidity and mortality. Univariate analysis indicated that an elevated serum LDH, low predicted forced vital capacity, low predicted forced expiratory volume in 1 sec (FEV_1) were significantly associated with the occurrence of a major complication. A multivariate logistic regression model indicated that a high LDH level, a low predicted FEV_1 and no extubation following surgery were associated independently with a postoperative major complication. Since only the complete removal of a tumor offers a chance for cure for the treatment of non-small cell lung cancer, it is sometimes necessary to perform a pneumonectomy for these high-risk patients. Patients identified as being at high risk of a major complication should be candidates for intensive preoperative evaluation and perioperative care.

KEY WORDS: **pneumonectomy, lung cancer, complication, multivariate analysis**

INTRODUCTION

The complete surgical removal of a tumor offers the best chance for a cure in patients with non-small cell lung cancer. Although recent advances in surgical technique using the bronchoplastic procedure have reduced the incidence of pneumonectomy, there are still many patients whose tumors require pneumonectomy, an operation first reported by Graham and Singer in 1933 [1]. However, pneumonectomy is associated with the highest morbidity and mortality rates compared to all other types of pulmonary resection. The 30-day mortality rate has been reported to be as high as 17% [2–6]. In a large series conducted by the Lung Cancer Study Group, the mortality rate associated with 569 pneumonectomies was reported to be 6.2%, while that associated with 1,058 lobectomies was 2.9% [7].

Efforts have been made to identify the factors that

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predict the occurrence of postoperative complications following the pneumonectomy [2,6,8–10]. However, since there are many potential variables often interrelated, it is difficult to extract which of these factors independently affect the outcome. A multivariate analysis is necessary which is able to evaluate how much variables increase probability of occurrence of mortality or morbidity. There is only one such analysis in the literature for a pneumonectomy [9].

In this study, we performed a detailed analysis of 62 patients who underwent pneumonectomy for the treatment of lung cancer at our department. We used a multivariate logistic regression model to evaluate which of 43 perioperative variables is predictive of postoperative complications or operative mortality.

MATERIALS AND METHODS

Patients and Clinical Data

During the 14-year period from January 1979 to December 1992, 429 patients with primary lung cancer underwent pulmonary resection at the Department of Surgery II, University of Occupational and Environmental Health, Japan. Of them, 62 patients underwent pneumonectomy. The charts of these patients were reviewed retrospectively. There were 56 male and 6 female patients with an average age of 61.5 years (range, 27 to 78 years). A right pneumonectomy was performed in 33 patients (53%), while a left pneumonectomy was performed in remaining 29 patients.

According to the TNM classification [11], all the patients were staged by conventional chest radiography, tomography, chest and abdominal computed tomographic (CT) scanning, and bone scintigram. All the patients had a preoperative checkup which included complete blood count, serum chemistry, creatinine clearance, pulmonary function test, arterial blood-gas determination, and electrocardiogram (ECG). The prediction of postoperative forced vital capacity (FVC) or forced expiratory volume in 1 sec (FEV_1) was calculated using the following formula:

$$\text{Postoperative FVC or } FEV_1 = R \times \text{preoperative FVC or } FEV_1$$

where R is the preoperative percentage of ventilation in the remaining lung, as determined by a pulmonary ventilation scan, performed routinely during the past 2 years. When the data on the ventilation scan were not available, they were estimated using a modified formula of Nakahara et al. [4]

$$R = 1 - (a - n/18 - n)$$

where a is 10 for right pneumonectomy and 8 for left pneumonectomy, and n is the number of obstructed segments in the affected lung. We evaluated 43 variables listed in Table I for postoperative morbidity and mortality.

TABLE I. Variables Evaluated for Morbidity and Mortality

General preoperative conditions (25 variables)
Age, sex, obesity (>20%), emaciation (>20%), performance status, Brinkman index, preoperative smoking cessation at least 2 weeks before surgery in patients who smoked, presence of preexisting hypertension or diabetes, hemoglobin level, white blood cell count, serum albumin level, serum LDH level, serum GPT level, creatinine clearance, % FVC, % FEV_1, FEV_1% (= (FVC/FEV_1 × 100) predicted % FVC, predicted % FEV_1, arterial pO_2, arterial pCO_2, ECG abnormality, ejection fraction as determined by echocardiography, preoperative chemo- and/or radiotherapy, presence of mediastinoscopic examination
Surgical factors (11 variables)
Year of operation (1980–1990 or 1991–1992), operation time, anesthesia time, estimated blood loss, water balance (intraoperative fluid intake—blood loss and urine volume), use of mechanical stapling device for bronchial stump closure, use of Novafil suture (monofilament polybutester suture) for bronchial stump closure, pericardiotomy, extubation when leaving the operating room, extent of lymph node dissection, curability of the operation
Tumor characteristics (7 variables)
Pathological T,N,M, tumor diameter, pathological stage, squamous cell histology versus nonsquamous, small cell carcinoma versus non-small cell carcinoma

Statistics

Uni- and multivariate analysis of the logistic regression model were used for analysis of the contribution of each variable to the occurrence of various complications. All analyses were performed using the PROC LOGIST routines of the SAS program library [12]. When the two-tailed *P*-value was <0.05, the variable was considered a significant contributor.

RESULTS

We experienced 89 postoperative complications in 39 of 62 patients (63%) (Table II). Respiratory complication occurred in 21 patients (34%), circulatory complication in 23 (37%), a bronchopleural fistula in 9 (15%), postoperative bleeding requiring thoracotomy in 3 (5%), a psychiatric disturbance in 6 (10%), and chylothorax in one (2%). The most frequent complication was supraventricular tachyarrhythmia that occurred in 21 cases (34%). Three patients died during the first 30 days after the operation (5%). The causes of these three deaths were respiratory failure, pulmonary embolism and bronchopleural fistula. Including these three patients, 13 of the patients (21%) eventually died of postoperative complication (survival range, 7–562 days, median 67 days), which was defined as a surgery-related death (Table II). A major complication, requiring a repeat thoracotomy or causing death, occurred in 19 patients (31%) (Table II).

TABLE II. Postoperative Complications in Patients With Pneumonectomy and Their Incidence

Complication	No. of patients	(%)	Reoperation	Operation-related death
Respiratory	21	(34)		
Pneumonia	9	(15)		6
Respiratory failure or ARDS	9	(15)		9
Bronchopleural fistula	9	(15)	9	5
Empyema thoracis	11	(18)	10	6
Sputum retention[a]	4	(7)		
Pulmonary embolism	1	(2)		1
Pulmonary edema	3	(5)		2
Circulatory	23	(37)		
Supraventricular arrhythmia	21	(35)		
Ventricular arrhythmia	4	(7)		
Miscellaneous				
Bleeding	3	(5)	3	
Wound infection	1	(2)	1	
Chylothorax	1	(2)	1	
Psychiatric disorder	6	(10)		
Recurrent laryngeal nerve palsy	4	(7)		

[a]Necessitating bronchoscopic suction.

TABLE III. Univariate Analysis of Perioperative Variables Contributing Occurrence of Major Complication Following Pneumonectomy*

Variable	Category	N	Odds ratio	*P*
Performance status			0.39	0.0201
Smoking index[a]			0.43	0.0662
LDH	<178	51	1.00	
	≧178	8	3.30	0.0069
%FEV_1	≧70	47	1.00	
	<70	9	2.15	0.0438
Predicted FVC	≧45	47	1.00	
	<45	9	2.15	0.0438
Predicted FEV_1	≧45	39	1.00	
	<45	17	2.02	0.0286
pO_2	≧75	44	1.00	
	<75	11	1.58	0.0896
Time of operation	1980–1990	32	1.00	
	1991–1992	30	0.60	0.0833
Pericardium opening	No	25	1.00	
	Yes	36	0.55	0.0429
Extubation	No	32	1.00	
	Yes	27	0.40	0.0099
N stage			0.71	0.0093

*Only the variables whose *P*-values were <0.1 were shown.
[a]In a unit of 500.

Among the 43 variables studied, univariate analysis indicated that the factors related significantly to a major complication were a serum lactic dehydrogenase (LDH) of >178 U/L, a predicted FVC of <45%, a predicted FEV_1 of <45%, and no extubation (Table III). We have created a model using multivariate logistic regression analysis for the prediction of postoperative major complications. Table IV summarizes these results and indicates that a serum LDH value of >178 U/L, a predicted FEV_1 of <45%, and no extubation following the operation all contributed independently to the occurrence of postoperative complications. Although the univariate analysis also indicated that poorer performance status, intrapericardial pneumonectomy, or higher N stage might have a lower risk of major complications, these three variables were not considered to be significant by the multivariate analysis as expected.

Since a bronchopleural fistula (BPF) is one of the most difficult complications following a pneumonectomy, we evaluated the factors separately that contributed to the occurrence of this complication. A BPF occurred in six patients (14.5%), six of whom eventually died of fistula-related complications despite undergoing various treatments. Univariate analysis indicated that a serum GPT of >40 U/L ($P = 0.0245$), a FEV_1 % of <60% ($P = 0.0211$), and no extubation following the operation ($P = 0.0492$) were associated with the occurrence of a BPF. However, multivariate analysis indicated that the predicted FEV_1% was the only independent variable predictive for the BPF. We also noted that in four of the nine patients (44%), BPF occurred on the thirtieth postoperative day or later.

DISCUSSION

In our study, the most common complication after pneumonectomy was cardiac arrhythmia (34%). In a recent analysis of cardiac arrhythmia following thoracotomy by von Knorring et al. [10], a pneumonectomy is associated twice as often with the development of arrhythmia than with any of the other operations (23% vs. 12%). Krowka et al. [3] had a similar experience. They found

TABLE IV. Multivariate Analysis of Variables Contributing to Occurrence of Major Complications Following Pneumonectomy

Variables	Category	Odds ratio	*P*
LDH	<178	1.00	
	≧178	8.21	0.0049
Predicted %FEV_1	≧45	1.00	
	<45	3.34	0.0120
Extubation	No	1.00	
	Yes	0.20	0.0099

that 22% of their patients who had undergone a pneumonectomy had a cardiac arrhythmia. All these arrhythmias were supraventricular in origin [3]. Although these investigators reported that onset of an arrhythmia following a pneumonectomy is associated with an increased mortality [3], this was not observed in our study—only 1 of 23 patients with an arrhythmia died within 30 days of the operation, while 2 of 39 patients without an arrhythmia also died.

We analyzed our data using a multivariate logistic regression model to search for factors predictive of morbidity and mortality. A predicted FEV_1 of <45%, no extubation following the operation, and a high serum LDH level were independently associated with the occurrence of a major postoperative complication. In an analysis of 197 patients who underwent elective pneumonectomy for neoplastic disease, Patel et al. [9] found that in-hospital mortality is associated with the presence of coexisting medical conditions, a preoperative FEV_1% of <55%, a 24-hr fluid replacement of >3 L, the presence of postoperative pulmonary edema, a respiratory tract infection, postoperative renal failure, and cardiac arrhythmias [9]. Unlike our analysis, their endpoint was mortality; postoperative complications were therefore listed as contributing factors. By contrast, Wahi et al. [6] have pointed out that patients who had a right pneumonectomy, combined chest wall resection, or an extrapleural pneumonectomy, a predicted FEV_1 of <1.65L or 58%, or a predicted FVC of <2.5L or 60% were at significantly increased risk of operative mortality.

Although there are some discrepancies in the details, these three studies, which include the present study, agree that pulmonary function, as determined by spirogram, is one of the most important variables that is predictive of postoperative morbidity or mortality. Nakahara et al. [4] found that the predicted postoperative %FEV_1 is a better variable than the predicted %VC and that all patients with predicted %FEV_1 less than 30% needed mechanical ventilation following lung resection. By contrast, Keagy et al. [2] stated that FVC, FEV_1, and FEV_1% showed no correlation with postoperative morbidity and mortality in patients undergoing pneumonectomy. This discrepancy may be at least partly due to the fact that they did not evaluate the predicted value following the operation, and that they did not adjust the value for the size of the patients.

In our analysis, the serum LDH level was associated strongly with postoperative morbidity. We currently have no explanation for this. To our knowledge, there have been no studies to date which analyzed the value of the serum LDH level for predicting postoperative morbidity or mortality. It remains to be determined how LDH level affects the occurrence of postoperative complications in a prospective fashion. Our study also indicated that the patient should be extubated as soon as possible following a pneumonectomy to avoid postoperative morbidity. This result also can be interpreted to mean that a positive airway pressure significantly increases the risk of morbidity or that a pneumonectomy should be avoided in patients whose pulmonary function is likely to require postoperative mechanical ventilation.

A bronchopleural fistula (BPF) is one of the most difficult complication following a pneumonectomy and is often associated with mortality. Asamura et al. [13] reported that from their analysis of 1,360 pulmonary resections for lung cancer, a pneumonectomy, residual cancerous tissue at the bronchial stump, preoperative irradiation, and diabetes are all independently associated with the subsequent development of a BPF. However, in our study these variables were not contributing factors and multivariate analysis indicated that a low FEV_1% was the only variable predictive for a BPF. There was a tendency for a postoperative BPF to be more common following a right pneumonectomy (7/33 following a right pneumonectomy versus 2/29 in left pneumonectomy), as has been previously reported [9].

We conclude that the postoperative predicted pulmonary function, especially %FEV_1, is most predictive of postoperative morbidity. Since only the complete removal of the tumor offers a chance for cure in the treatment of non-small cell lung cancer, it is sometimes necessary to perform a pneumonectomy in a patient at high risk for postoperative complications. Patients identified at high risk should be candidates for intensive preoperative evaluation and perioperative care. Furthermore, patients who undergo a pneumonectomy should have long-term close follow-up evaluation, because a BPF may occur late in the postoperative period.

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